Efficacy and safety of nintedanib in patients with idiopathic pulmonary fibrosis (IPF) and multiple comorbidities

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Introduction

- Patients with IPF frequently have comorbidities that may complicate the course of their disease, impair quality of life and affect adherence to medications.[1]
- The presence of comorbidities may influence decisions about the use of antifibrotic therapy.
- Nintedanib is an approved treatment for IPF that slows disease progression by reducing decline in forced vital capacity (FVC), with a side-effect profile characterized mainly by gastrointestinal events.[2]

Aim

- To assess the efficacy and safety of nintedanib in patients with IPF and multiple comorbidities.

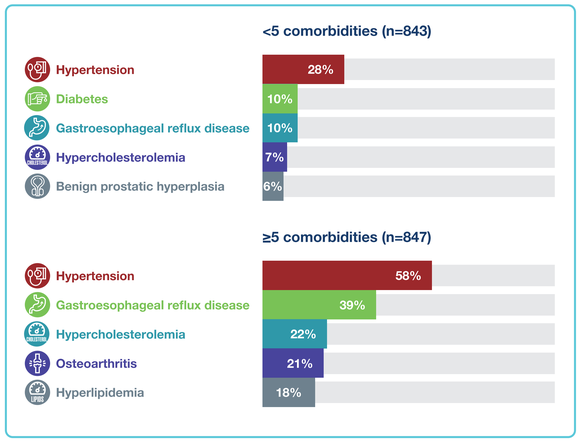
Methods

- Data were pooled from the placebo-controlled periods of five clinical trials of nintedanib: the Phase II TOMORROW trial (52 weeks),[3] the two Phase III INPULSIS trials (52 weeks),[2] the INMARK trial (12 weeks)[4] and a Phase IIIb trial (approximately 6 months).[5]
- In subgroups of patients with <5 versus ≥5 comorbidities (i.e. below and at least the median number of comorbidities) at baseline, we analyzed the following:
  - Annual rate of decline in FVC (mL/year)
  - Change from baseline in St George's Respiratory Questionnaire (SGRQ) total score (a measure of health-related quality of life)
  - Time to first acute exacerbation (investigator-reported)
  - Time to death
  - Adverse events.

Results

Patients

Most frequent comorbidities in patients with <5 and ≥5 comorbidities at baseline.



Baseline characteristics of patients with <5 and ≥5 comorbidities at baseline

Comorbidities	Male (%)		Age (years)		BMI (kg/m²)		Years since diagnosis of IPF	
	<5	≥5	<5	≥5	<5	≥5	<5	≥5
	80	75	65.5	69.2	26.9	28.9	1.4	1.5
	Former or current smoker (%)		FVC % predicted		DLco % predicted		SGRQ total score	
	70	74	79.6	79.5	47.3	48.3	37.6	42.0

Mean or % of patients

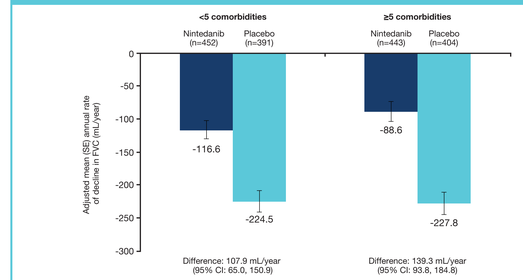
Exposure

- Mean (SD) exposure to nintedanib and placebo was 8.8 (4.1) and 8.2 (4.3) months in patients with ≥5 comorbidities and 9.2 (4.1) and 8.1 (4.4) months in patients with <5 comorbidities at baseline, respectively.

Annual rate of decline in FVC

- Nintedanib reduced the annual rate of decline in FVC (mL/year) in patients with <5 and ≥5 comorbidities at baseline, with no significant difference in its treatment effect between the subgroups.

Annual rate of decline in FVC (mL/year) in patients with <5 and ≥5 comorbidities at baseline

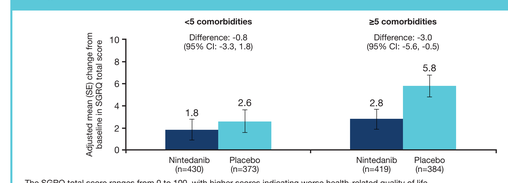


Treatment-by-time-by-subgroup interaction p=0.41.

Change in SGRQ total score

- Over 52 weeks, SGRQ total score increased (worsened) to a greater extent in patients with ≥5 than <5 comorbidities at baseline, particularly in the placebo group.

Change in SGRQ total score at week 52 in patients with <5 and ≥5 comorbidities at baseline



The SGRQ total score ranges from 0 to 100, with higher scores indicating worse health-related quality of life.
Treatment-by-subgroup interaction p=0.22.

Acute exacerbations and deaths

- The effect of nintedanib versus placebo in reducing the risk of a first acute exacerbation and the risk of death was consistent between patients with <5 and ≥5 comorbidities at baseline.

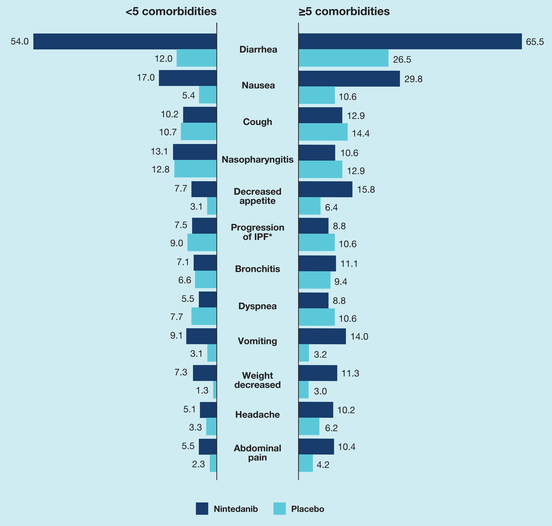
Time to first acute exacerbation and death in patients with <5 and ≥5 comorbidities at baseline

	<5 comorbidities		≥5 comorbidities	
	Nintedanib (n=452)	Placebo (n=391)	Nintedanib (n=443)	Placebo (n=404)
Patients with ≥1 acute exacerbation, n (%)	16 (3.5)	18 (4.6)	19 (4.3)	28 (6.9)
Hazard ratio (95% CI)	0.56 (0.28, 1.10)		0.53 (0.30, 0.96)	
Treatment-by-subgroup interaction	p=0.87			
Patients who died, n (%)	17 (3.8)	21 (5.4)	26 (5.9)	25 (6.2)
Hazard ratio (95% CI)	0.51 (0.27, 0.99)		0.85 (0.49, 1.48)	
Treatment-by-subgroup interaction	p=0.24			

Adverse events

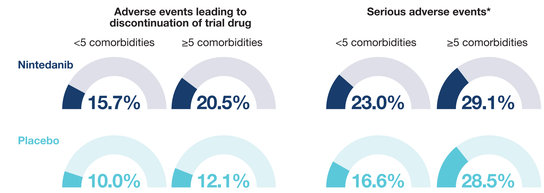
- The adverse event profile of nintedanib was similar between subgroups by number of comorbidities at baseline. In both treatment groups, diarrhea and nausea were reported more frequently in patients with ≥5 than <5 comorbidities at baseline.

Most frequent adverse events in patients with <5 and ≥5 comorbidities at baseline



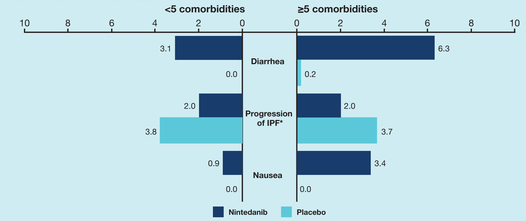
Data are % of patients with ≥1 such adverse event reported (irrespective of causality) in >10% of patients in either subgroup, coded using preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA).
*Corresponded to MedDRA term 'IPF', which included disease worsening and acute exacerbations of IPF.

Proportions of patients with adverse events leading to discontinuation of trial drug and severe adverse events in patients with <5 and ≥5 comorbidities at baseline



Data are % of subjects with ≥1 such adverse event. *Events that resulted in death, were life-threatening, resulted in hospitalization or prolonged hospitalization, resulted in persistent or clinically significant disability or incapacity, were a congenital anomaly or birth defect, or were deemed serious for any other reason.

Most frequent adverse events leading to discontinuation of trial drug in patients with <5 and ≥5 comorbidities at baseline



Data are % of patients with ≥1 adverse event leading to discontinuation of trial drug. Events reported in >2% of patients in either subgroup are shown. *Corresponded to MedDRA term 'IPF', which included disease worsening and acute exacerbations of IPF.

Conclusions

- **Nintedanib had the same benefit in reducing the progression of IPF in patients with ≥5 and <5 comorbidities at baseline.**
- **Discontinuation of nintedanib due to adverse events was more common in patients with ≥5 than <5 comorbidities at baseline.**
- **The identification and treatment of comorbidities are important aspects of the management of patients with IPF.**

References

1. King CS and Nathan SD. Lancet Respir Med 2017;5:72–84.
2. Richeldi L et al. N Engl J Med 2014;370:2071–82.
3. Richeldi L et al. N Engl J Med 2011;365:1079–87.
4. Maher TM et al. Lancet Respir Med 2019;7:771–79.
5. Lancaster L et al. Am J Respir Crit Care Med 2018;197:A4266.

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